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Effects of adding midazolam to ketamine and fentanyl combination in a burn wound dressing in adults

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Abstract

Aim: It was aimed to investigate the effects and side effects of adding midazolam to ketamine and fentanyl combination on sedation, hemodynamic stability and recovery rate during burn debridement and dressing in adult patients.

Material and Methods: ASA I-II group, adult patients aged between 18-70 years, who were going to undergo therapeutic procedures such as change of burn dressings and debridement, were included in the study. The cases were randomly divided into two groups. The ketamine/fentanyl group (Group KF) received 1 mg/kg ketamine i.v and 1 mcgr/kg fentanyl just before the dressing. In the ketamine+midazolam/fentanyl group (Group MKF), 0.03 mg/kg midazolam was additionally administered 10 minutes before the procedure. Systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), peripheral oxygen saturation (sPO2), respiratory rate (RR) were monitored and recorded every 5 minutes. The results were evaluated at the 95% confidence interval and the significance level was $p<0.05$.

Results: Fifty-nine patients aged between 15-56 years (29.98±9.22 years) were included in the study. Six patients (10.2%) were female and 53 (89.8%) were male. There was no statistically significant difference between the KF-MKF groups in terms of age, weight and gender, burn rate, ASA distribution, dressing time, and additional dose requirement values ($p>0.05$). SBP0, SBP5, SBP10, SBP15 values, DBP0, DBP5 values and HR0, HR5 values of the subjects in the KF group were found to be statistically significantly higher than the values of subjects in the MKF group ($p<0.05$).

Discussion: Combinations of midazolam-ketamine/fentanyl and ketamine/fentanyl provide effective sedation in burn debridement and dressing in adult patients. It was concluded that the addition of midazolam to the ketamine/fentanyl combination provides better hemodynamic stability.

Keywords
Midazolam, Ketamine, Dressing, Burn

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Introduction

Burn injury is a serious insult, and burn pain is considered by patients to be the most severe form of acute pain experienced. Burn-related pain occurs following burn insult as acute pain is closely related to the extent and extent of the injury. In addition to the burn injury, it can continue with repetitive treatment applications such as dressing changes, surgeries and physiotherapy applications during the treatment process, and in some cases, it turns into chronic pain. Burn pain also shows personal differences, and a person's psychosocial environment makes pain more complex. Effective pain control is an important problem in burn units and its treatment requires a multidisciplinary approach [1, 2].

Burn patients, unlike other insults, often experience recurring situations that can cause serious pain such as dressing and debridement. Although many methods have been reported to relieve pain arising during these therapeutic applications, there is no consensus as to which method is best in this regard. Different agents are used in different centers. Generally, ketamine is the preferred agent for burn dressings and debridements. Ketamine has a sedative and analgesic effect, does not cause respiratory depression, and can also be administered alone or in combination with intravenous/ inhalation anesthetics. It has been reported that even at subanesthetic doses, ketamine produces sufficient analgesia for burn dressing and burn wound debridement [3]. However, it has side effects such as hallucination on awakening, a rapid development of tolerance, a long recovery period and nausea. The addition of midazolam to ketamine has been reported to reduce the undesirable psychomimetic effects of ketamine [4]. In our study, it was aimed to investigate the effects and side effects of adding midazolam to ketamine and fentanyl combination during burn debridement and dressing in adult patients on sedation, hemodynamic stability and recovery rate, using the Ramsey sedation scale and modified Aldrete recovery score.

Material and Methods

With the approval of Kocaeli University Clinical Research Ethics Committee (KOÜ KAEK 2013/95), therapeutic procedures such as changing burn dressings and debridement will be performed, 59 adult patients aged between 18-70 years with ASA I-II group, 10-40% burns, 2nd and 3rd-degree burns and no burns in areas that could interact with the airway were included in the study. Pregnant, opioid allergy patients, and patients with significant psychiatric, cardiovascular, renal or hepatic disease were excluded from the study.

The cases were randomly divided into two equal groups considering the burn group and the percentage. The ketamine+midazolam/fentanyl group (Group MKF) received 0.03mg/kg midazolam 10 minutes before the procedure, and 1 mg/kg ketamine i.v. and 1 mcgr/kg fentanyl just before the dressing. In the ketamine/fentanyl group (Group KF), 1 mg/kg ketamine i.v. and 1mcgr/kg fentanyl were administered just before the dressing.

In the patients who were taken to the operating room, systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), peripheral oxygen saturation (sPO2), respiratory rate (RR) were monitored from the appropriate arm or leg and recorded every 5 minutes. When SBP was <80 mmHg, 10 ml/kg of saline 0.9% was administered. When the patient developed respiratory apnea, the Ambu mask was used. Hemodynamic changes (tachycardia, bradycardia), number of patients requiring additional ketamine, sedation score, dressing time, recovery times, and adverse effects such as nausea, vomiting, hypotension, hypertension, apnea, if any, were recorded. The Ramsey Sedation Score (RSS) was aimed to be >4 during the procedure.

Ketamine (0.5-1 mg/kg i.v.) was administered as rescue analgesia in cases of insufficient analgesia such as grimacing, movement in the extremities, and an increase in systolic blood pressure more than 25% above the baseline value. After sedation, patients with a modified Aldrete recovery score of 11 and above were taken to the service from the recovery room.

Statistical analysis

While evaluating the findings obtained in the study, statistical analyses were performed using IBM SPSS Statistics 22. The Mann-Whitney U test, Independent-Samples T-test, Paired Samples T-test and the Wilcoxon test were used for numerical data, and the Chi-Square test was used to analyze discrete variables. The results were evaluated at the 95% confidence interval and the significance level was $p<0.05$.

Results

Fifty-nine patients aged between 15-56 years (29.98±9.22 years) were included in the study. Six patients (10.2%) were female and 53 (89.8%) were male. There was no statistically significant difference between the KF-MKF groups in terms of age, weight and gender, burn rate, ASA distribution, dressing time and additional dose requirement values ($p>0.05$) (Table 1). It was determined that the SBP0, SBP5, SBP10 and SBP15 values of the subjects in the KF group were statistically significantly higher than the values of the subjects in the MKF group ($p<0.05$) (Table 2).

The DBP0 and DBP5 values of the subjects in the KF group were found to be statistically significantly higher than the values of the subjects in the MKF group ($p<0.05$). It was determined that the HR0 and HR5 values of the subjects in the KF group were statistically significantly higher than the values of the subjects in the MKF group ($p<0.05$) (Table 2).

Table 1. Data on demographic variables of groups

		Group KF (n=29)	Group MKF (n=30)	p
Age (year)		29.69±8	30.27±10.4	0.790
Gender	Male	25 (86.2)	28 (93.3)	0.424
	Female	4 (13.8)	2 (6.7)	
ASA	ASA1	26 (89.7)	27 (90.0)	0.965
	ASA2	3 (10.3)	3 (10.0)	
Weight (kg)		72.4±15	70.5±13.9	0.476
Burn Agent		28.9±11.3	28±19	0.336
Dressing time		25±14.8	22.5±6.5	0.835
Additional dose needed	Yes	12 (41.4)	10 (33.3)	0.712
	No	17 (58.6)	20(66.7)	

Group MKF: midazolam + ketamine / fentanyl group, Group KF: ketamine / fentanyl group. Mann-Whitney U test: values are given as mean ± standard deviation (median). Independent Samples T- test: values are given as mean ± standard deviation (median). Pearson's chi-square test: values are given as frequency (percentage)

Table 2. Comparison of Systolic blood pressure (SBP), Diastolic blood pressure (DBP) and Heart rate (HR) values.

	KF	MKF	p
SKB0	149.39±22.22	124.33±18.83	0.000*
SKB5	163.62±30.24	131.47±24.09	0.000*
SKB10	161.11±27.71	141.50±24.52	0.005*
SKB15	157.50±26.73	139.90±26.60	0.020*
SKB20	138.78±21.30	145.74±22.62	0.322
SKB25	155.18±26.49	142.92±27.77	0.283
SKB30	146.20±27.44	144.75±36.68	0.925
DKB0	85.50±16.19	71.17±12.27	0.000*
DKB5	93.76±13.10	79.73±13.99	0.000*
DKB10	89.57±14.26	85.87±12.20	0.291
DKB15	87.92±12.93	83.55±12.65	0.221
DKB20	84.61±13.99	86.43±12.63	0.664
DKB25	80.00±12.52	86.15±13.44	0.261
DKB30	80.40±12.21	83.25±17.40	0.688
KAH0	110.38±20.09	99.14±15.13	0.019*
KAH5	113.10±18.05	103.60±11.89	0.020*
KAH10	112.64±20.97	104.00±17.09	0.090
KAH15	111.67±22.16	107.10±15.66	0.401
KAH20	114.11±18.17	105.00±15.47	0.091
KAH25	105.55±17.06	107.54±16.29	0.773
KAH30	104.20±14.83	110.88±18.04	0.401

Mann- Whitney U test: values are given as mean ± standard deviation (median)
Independent Samples T-test: values are given as mean ± standard deviation (median)
*p<0.05

Table 3. Comparison of respiratory rate (RR) and peripheral oxygen saturation (sPO2) values.

	KF	MKF	p
SS0	21.17±5.64	17.72±3.67	0.010*
SS5	23.08±6.06	17.29±4.59	0.000*
SS10	23.43±5.14	19.17±4.80	0.003*
SS15	21.53±5.23	19.96±5.22	0.320
SS20	21.43±5.84	19.09±4.98	0.202
SS25	18.43±7.44	18.69±3.15	0.931
SS30	18.71±6.10	18.88±3.80	0.951
SPO20	96.69±3.47	97.76±2.21	0.467
SPO25	98.24±2.40	98.33±2.09	0.676
SPO210	97.89±2.97	98.43±2.06	0.955
SPO215	97.96±3.13	98.97±1.18	0.546
SPO220	97.28±3.18	99.17±1.03	0.058
SPO225	96.55±2.62	99.07±1.21	0.008*
SPO230	96.50±2.07	98.11±1.62	0.078

Mann- Whitney U test: values are given as mean ± standard deviation (median)
Independent Samples T -test: values are given as mean ± standard deviation (median)
*p<0.05

It was determined that the SS0, SS5 and SS10 values of the subjects in the KF group were statistically significantly higher than the values of the subjects in the MKF group (p<0.05). It was determined that the SPO225 value of the subjects in the KF group was statistically significantly higher than the values of the subjects in the MKF group (p<0.05) (Table 3).

Discussion

Burn insult is a painful trauma with long-term physical and psychological negative effects on patients, and patients are exposed to pain due to treatments such as burn dressing and physiotherapy during the treatment process. Burn-related pain first appears as acute pain. Dressing change, wound debridement and other interventional procedures applied to the patient increase pain formation and in some cases turn into chronic pain. Therefore, effective pain control is important in burn centers and the solution of this problem requires a multidisciplinary approach. Pain relief in burn patients should begin in the acute phase with insult and continue until the end of treatment. After the patient's acute pain has passed, the severity of the pain may increase depending on the treatment methods applied in the future, the presence of infection, rehabilitation applications, regeneration of damaged nerves and the psychosocial environment in which the person is located [1,5,6].

Burn pain can range from mild to severe, depending on the surface area and grade of the burn. Some studies have reported that the patient's pain at rest is partially mild, but the pain increases significantly during procedures such as dressing changes and physiotherapy [7].

Ketamine is the analogue of angel dust, and it is the closest drug to full anesthetic with its wide safety margin, providing amnesia, unconsciousness and analgesia. It disconnects the thalamus from the limbic cortex and provides clinically dissociative anesthesia. Unlike other IV anesthetics, it is preferred for sedation because it has fewer adverse effects on the cardiovascular and respiratory systems. [8] In addition to these positive effects, the patient may become agitated and hallucinate upon returning from the dissociative process. Hallucination is a common unwanted side effect of ketamine. In order to prevent this side effect, ketamine is often combined with an agent such as midazolam [9]. Midazolam is a frequently used agent in sedation due to its positive properties such as sedative, anxiolytic, sleep-inducing, anticonvulsant and central muscle relaxant effects, rapid onset of action, wide safety margin, and short recovery time. However, besides these positive effects, there are also undesirable side effects such as lack of analgesic property, rapid and excessive IV doses causing respiratory depression, hiccups, nausea, vomiting, excessive sedation, headache, and cough. Midazolam can be used for premedication purposes (anxiolytic, sedative and amnesic effect), for surgical or diagnostic interventions under regional anesthesia to provide sedation (sedative and amnesic effect), to provide induction and maintenance of anesthesia, to prevent convulsions (anticonvulsant effect). [10] Respiratory depression with midazolam and dysphoric reactions (irritability, depression, etc.) with ketamine may occur when midazolam and ketamine are used alone. When midazolam is used with ketamine, faster analgesia, amnesia, and fewer side effects occur [11].

Ketamine and fentanyl were used as analgesics in both groups in the study. For this purpose, we used midazolam, a short-acting benzodiazepine, at a dose of 0.03 mg/kg IV, so that the patient would not be sedated for a long time when the application was finished. Bowdle et al. stated that since fear and anxiety may develop in burn cases, the addition of anxiolytic or hypnotics such as benzodiazepines to analgesic treatment eliminates anxiety and reduces the amount of the agent to be used for analgesia [12]. Dachs et al. suggested that the addition of midazolam to ketamine reduces ketamine-related undesirable

effects such as unpleasant dreams and hallucinations [13]. We concluded that the addition of midazolam to the ketamine/fentanyl combination reduces the psychomimetic effects of ketamine.

The combination of midazolam with ketamine appears to be a good combination with short sedation and short recovery time. Aldrete or Modified Aldrete scoring is generally used during recovery in anesthesia applications. The modified Aldrete Score was used as the recovery score after dressing [14]. In our study, no statistically significant difference was found between the two groups in terms of recovery time, and the addition of midazolam to the ketamine/fentanyl combination did not prolong the recovery period.

Şentürk et al. investigated the effects of midazolam and ketamine combination and midazolam efficacy in oral premedication in children and their effects on possible hemodynamic and respiratory parameters, concluded that it can be used safely in pediatric premedication with its comfortable and easy application in children, providing effective sedation, facilitating anesthesia induction, and postoperative recovery [15]. Erk et al. reported that ketamine alone, with or without midazolam, provides a calm and safe anesthesia for pediatric patients in short-term procedures, and that the combination of ketamine and midazolam provides a better early postoperative period [16]. In our study, adequate sedation was achieved without midazolam, but adding midazolam provided better hemodynamics in terms of systolic blood pressure, diastolic blood pressure, and heart rate, especially in the early stages of the procedure.

Brecelj J et al. reported that the use of midazolam as a premedication before ketamine in pediatric patients is advantageous compared to the use of ketamine alone, as it reduces the occurrence of emergency reactions in the hospital [17]. In our study, the addition of midazolam reduced tachypnea in the early period in patients. Ghai B, et al. reported that oral midazolam alone and the combination of midazolam and ketamine provided equally effective anxiolysis and separation properties in children, however, the combination provided easy separation from their parents, providing a calmer and more relaxed state for the patient [18]. Dilli et al. concluded that the addition of midazolam to ketamine did not increase the frequency of side effects and that this combination was superior to ketamine alone in terms of sedation rate and parental satisfaction with sedation [19]. In our study, the addition of midazolam did not increase the dressing time and the need for additional doses. MacPherson et al. stated that the use of ketamine/midazolam is an effective pain control tool during burn dressings, and the incidence of side effects is low [20]. Our study supports these findings.

In conclusion, midazolam-ketamine/fentanyl and ketamine/fentanyl combinations provide effective sedation in burn debridement and dressing in adult patients. It was concluded that the addition of midazolam to the ketamine/fentanyl combination provides better hemodynamic stability.

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Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

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